CHAPTER 53 - Postmarketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products

SUBJECT:	IMPLEMENTATION DATE
POSTMARKETING ADVERSE DRUG EXPERIENCE (PADE) REPORTING INSPECTIONS	December 15, 2012
REVISION:	COMPLETION DATE December 15, 2015

DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
FACTS does not require product codes for postmarketing adverse drug experience (PADE) reporting inspections	53001A Adv Drug Experience Rptg Regs Center Initiated 53001B Adv Drug Experience Rptg Regs Field Initiated

FIELD REPORTING REQUIREMENTS:

A. PADE DOMESTIC INSPECTIONS

1. For potential OAI *domestic* inspections under PAC 53001, proceed as follows:

   a. Notify the Pharmacovigilance Compliance (PVC) Team in the Office of Compliance (OC), Office of Scientific Investigations (OSI) at CDER-OSI-ADE@FDA.HHS.GOV of any potential domestic OAI inspection results when 483 is available in Turbo EIR.

   b. Forward the following electronically to the PVC Team via the Case Management System (CMS):

      (i) The district regulatory action recommendation and supporting documents (e.g. draft Warning Letter)
      (ii) Establishment Inspection Report (EIR)
      (iii) Exhibits to the EIR
      (iv) Response from the firm, if any.

2. For potential VAI domestic inspections under PAC 53001, proceed as follows:

   a. Send notification to CDER-OSI-ADE@FDA.HHS.GOV, that the Form FDA 483 is available in Turbo EIR to the PVC Team after the close of inspection.

   b. Forward the following documents by mail or email to the PVC Team (the email address and the mailing address for the PVC Team can be found in PART VI, SECTION

C "CONTACTS"):

(i) Establishment Inspection Report (EIR) (if not available in TURBO)
(ii) Exhibits to the EIR
(iii) Response from the firm, if any

c. Enter the FDA Form 483 and EIR into TURBO within the timeframes established by your district's standard operating procedures (SOPs), not to exceed 60 days of closing the inspection.

3. For potential NAI domestic inspections under PAC 53001, proceed as follows:

a. Forward the following by mail or email to the PVC Team (the email address and the mailing address for the PVC Team can be found in PART VI, SECTION C "CONTACTS"):

(i) Response from the firm, if any
(ii) Exhibits to the EIR, if required

b. It is not necessary to routinely submit exhibits for domestic NAI inspections to the PVC Team. Submit exhibits for domestic NAI inspections to the PVC Team only when a firm responds in writing to an inspection, when significant discussion items have been identified during the inspection, or when requested by the PVC Team.

B. PADE FOREIGN INSPECTIONS

1. For all foreign PADE inspections, send the Form FDA 483 to the PVC Team after the close of the inspection.

2. The original EIR, printed from TURBO and signed, plus all original exhibits must be sent to the PVC Team point-of-contact (POC) identified in the FACTS assignment.

3. All firm written responses must be directed to the POC identified in the FACTS assignment.

4. The PVC Team will make the final inspection classification (e.g. OAI, NAI, VAI) for all foreign PADE inspections.

5. The PVC Team will author and issue all foreign Warning Letters (WL) and Untitled Letters (UL).

C. FOR ALL PADE INSPECTIONS

1. Enter all EIRs into TURBO within the timeframes established by your district's SOP. If the EIR cannot be completed within the specified timeframe, notify the PVC Team electronically at CDER-OSI-ADE@FDA.HHS.GOV.

2. For inspections conducted under multiple PAC codes, determine the classification of the

53001 Inspection and proceed as above.

3. For *all* inspections: If the Investigator issues a Form FDA 483 at the close of inspection, the notification that the 483 is available in Turbo EIR should be emailed to the PVC Team at CDER-OSI-ADE@FDA.HHS.GOV or faxed to 301-847-8748.

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PART I - BACKGROUND

Postmarketing safety data collection and adverse event reporting is a critical element of the Agency's Postmarketing safety surveillance program for FDA-regulated drug products. While many common and preventable risks are identified and evaluated before a product is marketed, some risks become evident only after a product is marketed and real-world experience with the product is documented. Postmarketing safety data collection encourages informed decision-making that maximizes benefits and minimizes risks to patients. The Agency's existing postmarketing safety reporting requirements for human marketed drugs and therapeutic biological products can be found at 21 CFR 310.305, 314.80, 314.98, 600.80, and 600.81. These regulations describe who must submit postmarketing safety reports to the Agency and how the reports should be submitted.

Postmarketing safety reporting requirements for over-the-counter (OTC) drugs marketed in the US without an approved application is governed by Public Law 109-462, Dietary Supplement and Nonprescription Drug Consumer Protection Act, which was signed into law on December 22, 2006. Prior to the enactment of Public Law 109-462, only OTC drugs marketed with an approved application were subject to mandatory postmarketing safety reporting requirements. However, under the Dietary Supplement and Nonprescription Drug Consumer Protection Act, the manufacture, packer, or distributor whose name appears on the label of a nonprescription drug marketed in the United States shall submit any report received of serious adverse event associated with such drug to the Agency within fifteen (15) business days.

The Agency currently is in the process of developing proposed rules to further amend safety reporting requirements for human drugs and therapeutic biological products. Questions concerning postmarketing safety reporting requirements should be addressed to CDER's Office of Compliance, Office of Scientific Investigations, Pharmacovigilance Compliance Team at CDER-OSI-ADE@FDA.HHS.GOV.

A. OBJECTIVES

The objectives of the PADE reporting compliance program are:

1. To assure that safe and effective human drugs are available to the American people.

2. To verify the accuracy, reliability, and timeliness of postmarketing data submitted to FDA.

3. To support medical reviewers within FDA by ensuring that they receive drug safety data required for the continual evaluation of product safety.

4. To monitor industry's compliance with the PADE reporting requirements.

B. APPLICABLE REGULATIONS

The PADE and safety reporting regulations are set forth in Title 21 of the Code of Federal Regulations (21 CFR) Sections 310.305, 314.80, 314.81(b)(2), 314.98, 314.540, 314.630, 600.80, 601.28, 601.44, 601.70, and 601.93, and in the Federal Food, Drug, and Cosmetic Act (FD&C Act) Chapter VII, Subchapter H, Section 760.

In general, this program does not cover postmarketing adverse drug experience reporting for veterinarian drugs, Investigational New Drug (IND) not approved in an application and biological products not covered by CDER.

C. COVERED PRODUCTS

The FD&C Act and applicable regulations cover postmarketing adverse event reporting for:

1. Prescription drugs and nonprescription drugs that have approved new drug applications (21 CFR 314.80 and 314.81);

2. Prescription drugs and nonprescription drugs that have approved abbreviated new drug applications (21 CFR 314.98 and 314.81);

3. "Subpart H" drugs approved under accelerated approval of new drugs for serious or life-threatening illnesses (21 CFR 314.540);

4. "Subpart I" drugs approved when human efficacy studies are not ethical or feasible (21 CFR 314.630);

5. Non-application nonprescription drug products (FD&C Act Chapter VII, Subchapter H, Section 760) (Over-the Counter (OTC) Monograph);

6. Licensed therapeutic biological products (21 CFR 600.80, 601.28, and 601.70);

7. Biological products approved under accelerated approval for serious or life-threatening illnesses (21 CFR 601.44);

8. Biological products approved when human efficacy studies are not ethical or feasible (21 CFR 601.93).

9. Marketed prescription drugs that are not the subject of approved applications (21 CFR 310.305)[1] . For this category, please notify the PVC Team at CDER-OSI-ADE@FDA.HHS.GOV for cases that may result in regulatory action recommendations.

[1] In June 2006, the Agency issued a revised Compliance Policy Guide (CPG) Section 440.100 entitled Marketed New Drugs Without Approved NDAs or ANDAs. This revised CPG articulates the agency's risk based enforcement

D. RESPONSIBLE FIRMS

Those responsible for reporting postmarketing adverse drug experiences to the Agency are referred to as "responsible firms". Responsible firms may perform some or all of the postmarketing adverse drug experience (PADE) reporting functions or may contract with other firms to perform some or all of their PADE reporting functions. However, responsible firms retain the regulatory obligation to ensure all PADE reporting activities are performed in accordance with the applicable FDA laws and regulations. Responsible firms include:

1. Holders of approved new drug applications (NDA) and abbreviated new drug applications (ANDA), including Positron Emission Tomography (PET) approved applications (effective 12/9/2011) (21 CFR 314.80, 314.81(b)(2), 314.98, 314.540, and 314.630);

2. Persons named as the manufacturer, packer, or distributor on the label of approved drug products (21 CFR 314.80, 314.98, 314.540, and 314.630);

3. Persons named as the manufacturer, packer, or distributor on the label of non-application prescription drugs (21 CFR 310.305);

4. Persons named as the manufacturer, packer, or distributor on the label of non-application nonprescription drugs (FD&C Act Chapter VII, Subchapter H, Section 760)[2]; and

5. Any person holding a biologics license (21 CFR 600.80, 601.44, 601.93, 601.28, and 601.70).

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approach with respect to marketed unapproved drugs. This approach is intended to protect the public health without imposing undue burdens on consumers or unnecessarily disrupting the market. (See CPG Section 440.100 for more information on the agency's approach to prioritizing enforcement actions with regard to the universe of unapproved marketed drug products.) Notify the PVC Team at CDER-OSI-ADE@FDA.HHS.GOV for all cases that may result in a regulatory action recommendation.

[2] FDC Act 760(b)(2) gives added responsibilities to a retailer whose name appears on the label as a distributor. A retailer/distributor may, by agreement, authorize the manufacturer or packer of the nonprescription drug to submit the required reports for such drugs to FDA provided that the retailer directs to the manufacturer or packer "all adverse events associated with the drug that are reported to the retailer through the address or telephone number described in section 502(x).

PART II - IMPLEMENTATION

A. OBJECTIVES

The PADE program covers domestic and foreign inspections of responsible firms and contractors working on their behalf. This section provides information to investigators for conducting regulatory inspections and follow-up. The objectives of the PADE program will be met by:

1. Assessing compliance with the PADE reporting requirements, and

2. Providing information to firms during inspections to encourage voluntary compliance with PADE requirements.

B. PROGRAM MANAGEMENT INSTRUCTIONS

1. Assignments: Each year, using a risk-based approach, the PVC Team selects firms to be inspected. The risk-based approach takes into account factors such as the date of the firm's last PADE inspection, the firm's past compliance history, identified deficiencies, acquisition of new drug approvals or abbreviated new drug approvals (A/NDAs), and product safety concerns. Other factors are considered as needed.

   a. The PVC Team will issue PADE inspection assignments to the District Office management via electronic mail and the Field Accomplishments and Compliance Tracking System (FACTS).

   b. The FACTS assignment will list the firm to be inspected and identify a point of contact (POC) on the PVC Team.

   c. At least two weeks prior to the initiation of each inspection, the Investigator must contact the PVC Team to determine if the PVC Team has identified specific concerns regarding the firm's compliance.

   d. A memorandum containing specific concerns suggested to be addressed during the inspection and background on the firm and its operations will be e-mailed to the District Office Investigations Branch Director, or designee, prior to the start of the inspection. Questions about the assignment or the memorandum should be addressed to the POC indicated in the FACTS assignment.

   e. If a PADE inspection is combined with any other inspection, the Investigator is encouraged to contact the PVC Team for additional information related to the adverse drug experience reporting compliance of this firm.

   f. Contact information for the PVC Team can be found in this document in PART VI,

SECTION C - CONTACTS.

2. Performance Goal Inspections: PADE reporting compliance inspection requests may be either performance goal (PG) or routine surveillance assignments. PG and routine surveillance inspection requests are generally issued at the start of the fiscal year.

   a. Performance Goal inspection requests can be identified by the letters "PG" in the subject line of the FACTS assignment.

   b. Routine surveillance inspection requests do not have a letter designation in the subject line of the FACTS assignment.

   c. Additional inspections, both performance goal and routine surveillance, may be assigned during the year to address new and emerging safety concerns. Such assignments are usually in response to new or emerging concerns from CDER's Office of Compliance (OC), Office of Surveillance and Epidemiology (OSE), Office of New Drugs (OND), Office of Generic Drugs (OGD), Office of Nonprescription Products (ONP), or District Offices.

3. District Office Responsibilities

   a. The District Offices are encourage to contact the PVC Team for additional information related to the inspected firm as close to the start of the inspection as possible.

   b. District staff may become aware of a need for additional information on a specific PADE complaint or may identify a potential PADE reporting concern during an inspection conducted under a different program. In these situations:

      (i) The District Investigator and Supervisor or Compliance Officer is encouraged to contact the PVC Team.
      (ii) The PVC Team may provide additional information relating to the inspected firm.
      (iii) The District Office should add PAC 53001B to the current FACTS assignment.

4. Follow-up assignments: The district is encouraged to contact the PVC Team prior to beginning any follow-up inspections in FACTS to receive additional information.

   a. The District Office should contact the PVC Team if the District Office intends to issue a follow up assignment in FACTS under PAC 53001B in response to findings from a previous ADE inspection.

   b. The District Office shall notify the PVC Team at CDER-OSI-ADE@FDA.HHS.GOV when possible, no later than 2 weeks prior to the scheduled start of the inspection. The PVC Team will provide additional information to the investigator at this time.

c. Follow-up inspections will be counted as performance goal inspections if issued by CDER as such.

5. Assignments not Completed:

a. Assignments not completed by the FACTS target date must be returned in FACTS to the issuing office.

b. Assignments not completed by the FACTS target date must not be conducted in the next fiscal year.

PART III – INSPECTIONS

Contents of Part III:

A. GENERAL

1. PADE inspections are conducted to determine compliance with the PADE and safety reporting requirements set forth in

   - Title 21 of the Code of Federal Regulations (21 CFR) Sections 310.305, 314.80, 314.81(b)(2), 314.98, 314.540, 314.630, 600.80, 601.28, 601.44, 601.70, and 601.93, and

   - the Federal Food Drug and Cosmetic Act (FD&C Act) Chapter VII, Subchapter H, Section 760 (this section of the Act went into effect on December 23, 2007.)

2. The PVC Team will select the sites for inspection and issue the assignments in FACTS to the District Offices. For assignments that are district-initiated, the District should contact the PVC Team at CDER-OSI-ADE@FDA.HHS.GOV prior to conducting the inspection to receive additional information related to the inspected firm. For complete information on inspection site selection, go to PART II, SECTION B, "PROGRAM MANAGEMENT INSTRUCTIONS."

B. PRODUCTS COVERED DURING INSPECTION

The PVC Team will issue an inspection assignment memorandum to the Investigator upon notification of pending inspection. The inspection assignment memorandum may identify specific products to receive priority coverage during the inspection. If the inspectional assignment memorandum does not identify specific products to receive priority, the Investigator should review the firm's files for its approved drug products, approved therapeutic biological products, OTC Monograph drugs, and any unapproved prescription drug products that the firm may be manufacturing, or, in the case of a contractor or affiliate, any of these types of products for which the firm is performing PADE reporting activities.

1. The Investigator should focus on products associated with the greatest potential or actual impact on public health, including products that:

   a. have an incomplete safety profile (e.g., products approved within the last three years or products with limited market exposure),

   b. have emerging safety issues (e.g., products with postmarketing requirements, postmarketing safety commitments, postmarketing safety studies, Risk Evaluation and Mitigation Strategies (REMS), or deemed REMS), or

   c. have a greater than average potential safety impact (e.g., products indicated for use in pediatric or other vulnerable populations, products with a narrow therapeutic index, or products with known safety risks).

2. The following is a list of resources that may be used to identify products to be covered during inspection. (For Internet URLs, please see PART VI, SECTION A, "REFERENCES.")

   a. Orange Book – FDA database contains the firm's approved drug products.

   b. NDC Directory – FDA database contains firm's marketed products.

   c. Drugs@FDA – FDA database contains the approval and marketing status of drugs.

   d. Postmarketing Requirements and Commitments – FDA database of PMRs and PMCs is updated quarterly, so may not reflect the current status of all commitments.

3. During the inspection, obtain a complete list of the firm's drug products, whether approved, unapproved, prescription, or non-prescription[3]. For each product, identify:

[3] Information collected during the inspection about drugs marketed outside the United States (US) may be relevant to FDA if the drugs are connected with adverse event reports and the drugs contain the same active moiety as a drug product marketed within the US.

a. the name of the firm(s) listed on the label as manufacturer, packer, or distributor,

b. the application approval date (if applicable),

c. the application status (approved, unapproved, pending approval, OTC monograph product etc.) and marketing status, and

d. name of the party responsible for PADE reporting.

C. WRITTEN PROCEDURES

Firms are required to have adequate written procedures for the surveillance, receipt, evaluation and reporting of PADE reports to FDA. Requirements pertaining to PADE written procedures are set forth in 21 CFR 310.305 and 314.80. During inspection, ask for an overview of the firm's pharmacovigilance activities and determine the adequacy of the firm's written procedures.

1. Review the firm's written procedures for surveillance, receipt, evaluation, and submission of adverse event data. Determine if these procedures are adequate to ensure complete, accurate, and timely PADE reporting to the Agency. Written procedures are to be easily available and followed by all employees involved in pharmacovigilance and all employees who may come into contact with potential postmarketing adverse event information (including legal staff, administrative support staff, sales representatives, professional and consumer information support staff, and contractors).

2. Determine if the firm's procedures address the handling of data that may be received outside of normal work hours or through electronic means, such as e-mail or website comment boards. Procedures should include instructions for documenting the actual date the information was provided to the firm.

3. There is an exception to the requirement for written procedures for non-application, non-prescription drugs, also known as OTC Monograph Drugs; *Unlike CFR 314.80, Section 760 of the Act does not require a firm to have written procedures.* If the firm markets any non-application, non-prescription drugs, evaluate the firm's compliance with PADE reporting requirements by following the instructions below in PART III, SECTION R, "ADE REPORTING REQUIREMENTS FOR OTC MONOGRAPH DRUGS."

4. If the firm out-sources any of its PADE reporting responsibilities to contractors, identify the names and business locations of the contractors, then follow the instructions below in PART III, SECTION U, "ADE COLLECTION & REPORTING BY NON-APPLICANTS."

5. If the firm co-markets or co-licenses any drug products and shares PADE reporting responsibilities with a business partner, follow the instructions below in PART III, SECTION I, "PHARMACOVIGILANCE AGREEMENTS AND SAFETY DATA EXCHANGE AGREEMENTS."

6. Requirements for record keeping and reporting of postmarketing adverse drug experiences associated with prescription drugs marketed for human use without an approved new drug application (NDA) can be found in 21 CFR 310.305. The requirements of 21 CFR 310.305 apply to any person whose name appears on the label as manufacturer, packer, or distributor.

7. All of the firm's employees who could foreseeably come into contact with postmarketing adverse event information should be able to identify a postmarketing adverse event, know the four basic elements required for reporting, and know how to convey the adverse event information to the firm's pharmacovigilance department for reporting to the Agency.

D. SOURCE DATA EXTRACTION

Review the firm's procedures for determining how information is extracted from the source documents for inclusion in reports submitted to the Agency. Determine if these procedures are adequate to ensure that all pertinent information is appropriately included in the reports. Review a representative amount of the firm's "Individual Case Safety Reports" (ICSRs) and compare data in the ICSRs to data in the source documents to ensure completeness and accuracy.

1. Spontaneous vs. Study AE Reporting: Adverse events may be classified as spontaneous or study, depending on how the firm received the adverse event information.

   a. Spontaneous AE reports are communications from an individual (e.g., health care professional, consumer) to a company or regulatory authority that describes a suspected adverse experience. Spontaneous reports do not include cases identified from information solicited by the firm.

   b. A study adverse event report is one that originates from any organized data collection system. Reports that originate from clinical trials, patient registries, pregnancy registries, company sponsored patient support programs, disease management programs, or postmarketing studies should handled as if they were study reports and not as spontaneous reports. See PART III, SECTION G. "POSTMARKETING STUDIES" for information on how adverse experiences derived from organized data collection systems should be reported to the Agency.

   c. The firm should have adequate written procedures for the management of both spontaneous and study reports of adverse events.

2. Expectedness: Review the firm's procedures for determining whether a reported adverse event is considered expected (labeled) or unexpected (unlabeled) as per the US Package Insert (PI). There is no requirement to determine expectedness for OTC Monograph products.

3. Seriousness: Review the firm's procedures for determining whether a reported adverse event is considered serious. The definition of a serious ADE is defined in regulation as any adverse drug experience occurring at any dose that results in any of the following outcomes:

   a. death,

   b. a life-threatening adverse drug experience,

   c. inpatient hospitalization or prolongation of existing hospitalization,

   d. persistent or significant disability/incapacity,

   e. a congenital anomaly/birth defect, or

   f. a medically important event that does not result in one of the above outcomes may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or require medical intervention to prevent one of the outcomes listed in this definition.

   Note: The term seriousness differs from severity. "Serious" has the regulatory definition above, while "severity" may be used to describe the extent of a condition, (e.g. severe cold, severe back pain). An event that is described using the word "severe" may or may not be serious, depending on the outcome of the event. The use of the word "severe" alone does not determine whether an event is "serious" for purposes of expedited submission of ADE reports.

4. Event Coding: Determine that the firm has procedures in place to consistently and accurately code ADEs (e.g., MedDRA coding).

5. Reporting: Determine if the firm is in possession of any ADE data that was not submitted to the Agency, as required.

6. 15-Day Alerts: Request the firm to provide a listing of all 15-Day Alert reports submitted late to the Agency. For each late report, the firm should provide justification for why the report(s) were late and an appropriate corrective action, if applicable.

   Note: If the Investigator finds that relevant information was omitted from or misrepresented in a report submitted to the Agency, obtain copies of the source documents and the submitted report; then notify the PVC Team.

E. WAIVERS

If the firm states that FDA granted a waiver for any AE reporting requirement, or part of the reporting process, obtain a copy of the waiver. Commonly issued waivers permit firms to

submit Periodic Safety Update Reports (PSURs) instead of Periodic Adverse Drug Experience Reports (PADERS), or exempt firms from submitting individual reports for non-serious labeled events. Most waivers cover a specific drug or biologic. When the ownership of an, NDA, ANDA or BLA changes, FDA accepts that the waiver applies to the new holder of the application.

F. FOLLOW-UP INFORMATION

Review the firm's procedures for obtaining, documenting and reporting follow-up information for adverse drug experiences. The firm should have procedures in place for the collection of the four basic data elements needed to submit a report (i.e., identifiable patient, identifiable reporter, suspect drug, and adverse drug experience) and adequate reporter contact information to allow for later follow-up.

G. POSTMARKETING STUDIES

A post-marketing study is any study designed to gather specific information about an approved drug. Post-marketing studies are initiated to better understand product use in real-world situations, to fulfill a specific regulatory requirement, or to monitor safety in a large, non-clinical trial setting.

FDA has determined that, for purposes of postmarketing safety reporting, information concerning adverse experiences derived during planned contacts and active solicitation of information from patients (e.g., patient registries, pregnancy registries, company sponsored patient support programs, disease management programs) should be handled as safety information obtained from a postmarketing study.

1. Applicants are not required to submit individual case safety reports obtained from postmarketing studies unless the adverse event is serious and unexpected *and there is a reasonable possibility that the drug caused the adverse experience.* (Reference: 21 CFR 310.305(c)(1)(ii), 314.80(c)(2)(iii), 314.80(e), 600.80(c)(2)(iii), and 600.80(e)). The firm’s written procedures should include a method adequate for determining and documenting the causal relationship between the drug and the adverse event.

2. Determine how the firm identifies and monitors all of its postmarketing studies, including non-applicant-sponsored clinical data obtained by the firm, to ensure that the firm’s pharmacovigilance department receives all potential PADEs.

3. The firm is responsible for reviewing all adverse events associated with the use of its approved drug product even if the approved product is not the primary study drug (e.g., if the approved product is used as a concomitant medication or as the comparator product in a study).

4. The initiation and status of postmarketing studies must be reported in Periodic Reports

and NDA Annual Reports as required by 21 CFR 314.80(c)(2) and 314.81(b)(2)(viii). During inspection, select a number of Periodic Reports and Annual Reports and confirm that the status of postmarketing studies are included in the reports.

H. IND TRIALS INVOLVING AN APPROVED DRUG PRODUCT

Adverse experiences occurring with approved drugs or biological products during IND trials must be submitted to the Agency as prescribed in 21 CFR 312.32, to the FDA new drug review division in CDER, or the product review office in CBER, that has responsibility for oversight of the IND. For all IND trials involving approved drug products, adverse experiences that are serious, unexpected, and possibly related to the product must also be reported to the NDA (if any) as required by 21 CFR 314.80(e).

1. During inspection, determine if the firm is in possession of any ADEs arising from the use of its approved drugs in clinical trials. If the ADEs are serious, unexpected, and possibly related to the drug, determine if the ADEs were reported to the NDA as expedited 15-day Alert reports.

2. Determine if adequate procedures are in place for the surveillance, receipt, evaluation, causality assessment, follow-up, and reporting of adverse event data related to the use of the approved product as required by 21 CFR 314.80(e).

I. PHARMACOVIGILANCE AGREEMENTS AND SAFETY DATA EXCHANGE AGREEMENTS

1. Review agreements between the firm and any other manufacturers, packers, distributors, affiliates, subsidiaries, contract research organizations (CROs), licensees, or parent companies to determine if the agreement adequately addresses the firm's pharmacovigilance and PADE reporting activities and regulatory responsibilities.

2. Determine how the firm verifies that any other firms processing adverse event data on its behalf are in compliance with PADE reporting regulations and are performing the PADE reporting activities established in the agreement.

3. If the inspected firm is a contractor, review the written agreement between the contractor and the firm with regulatory reporting responsibility. Determine if the contractor has adequate written procedures covering all PADE reporting activities that are being performed under contract.

J. CORPORATE TRANSITIONS

"Corporate transitions" can be defined as situations involving the transfer of drug approvals, the transfer of pharmacovigilance activities, corporate mergers, corporate restructuring, large scale personnel changes, or significant information technology (IT) changes such as new

computer systems or databases. When inspecting firms undergoing corporate transitions, determine that written procedures have been appropriately updated to ensure that the surveillance, receipt, evaluation, and reporting of PADEs remains in a state of compliance.

K. SPECIAL DISTRIBUTION SYSTEMS

If the firm, or any of its contractors, have special distribution programs, such as patient assistance programs, professional product sampling programs, or other marketing programs, review the firm's written procedures to determine if they adequately address the receipt, evaluation, and reporting of PADEs obtained through these programs. Information derived from special distribution systems should be handled as information derived from postmarketing studies, unless directed otherwise by the Agency. Reporting requirements for postmarketing studies, including special distribution arrangements, can be found in PART III, SECTION G, "POSTMARKETING STUDIES." A list of company-sponsored patient assistance programs can be found at Partnership for Prescription Assistance.

L. FOREIGN PADE REPORTING

1. The requirements for reporting foreign postmarketing adverse experiences can be found in 310.305(c)(1)(i), 314.80(c)(1)(iii) and 600.80(c)(1)(iii).

    a. Foreign reports of serious, unexpected adverse experiences must be submitted to FDA as 15-day Alert reports. Other foreign reports, including serious and expected, nonserious and unexpected, and nonserious and expected adverse experiences are not required to be submitted to the Agency.

    b. Reports of foreign serious, unexpected adverse experiences should be submitted for products that have the same active moiety as a product marketed in the United States. This is true even if the excipient, dosage forms, strengths, routes of administration, and indications vary.

    c. When a foreign report is submitted on a product that is not identical to a product marketed in the United States, item C1 of FDA Form 3500A should contain the foreign trade name, the generic name, and the NDA number for the product with the same active moiety that is marketed in the United States.

    d. For foreign reports, the 15-day time clock begins when the applicant or its foreign affiliate has received the four basic elements for a 15-day Alert report. Applicants should establish effective mechanisms to ensure rapid information transfer from their foreign affiliates.

2. Since 310.305 and 314.80 apply only to marketed prescription drugs without approved applications and approved application drug products, respectively, OTC drugs marketed in the United States without an approved application have no requirement to submit

foreign adverse experience reports to the Agency.

M. PADEs REPORTED TO THE FIRM'S LEGAL DEPARTMENT

1. PADE information may be received by a firm's legal department because of product litigation. The firm must have adequate written procedures for forwarding PADE information received by it's legal department to it's drug safety unit for reporting to the Agency as required by 21 CFR 314.80(b). The date that the legal department receives the PADE information becomes the clock-start date for reporting to FDA.

   Firms involved in mass tort litigation may request FDA to waive all or part of the firm's PADE reporting obligations, or to alter the timelines for reporting PADEs to the Agency. Requests for waivers must be submitted to the Agency in writing and are granted on a case-by-case basis for good cause shown. Refer to 21 CFR 314.90. If the firm claims to have a waiver for any part of its PADE reporting obligations, obtain a copy of the waiver. Review the waiver and determine if the firm is complying with the terms set forth by the Agency.

2. A firm may attempt to use the date that it forwards PADE information from its legal department to its drug safety unit as the clock-start date for ADE reporting purposes. This is unacceptable, unless an Agency waiver was obtained in advance.

N. SCIENTIFIC LITERATURE REPORTS

Determine if the firm reviews scientific literature for postmarketing adverse drug experiences. If the firm obtains adverse drug experience information from scientific literature, the firm must report serious and unexpected PADEs to the agency within fifteen calendar days, accompanied by a copy of the source article, as required by 21 CFR 314.80(d). Literature articles should be submitted to the Agency in English.

O. COMPLAINT FILES

Request a list of the firm's open or pending complaint files. Select a representative number of complaints and determine how the firm evaluates the complaints to determine if a PADE report is required to be submitted to the Agency.

P. PERIODIC SAFETY REPORTS

Determine if the firm is submitting quarterly and annual Periodic Reports as required by 21 CFR 314.80(c)(2) and 600.80(c)(2) to FDA, within the required timeframes, for its approved products.

1. Firms are required to submit Periodic Reports at quarterly intervals for the first three years from the date of approval, and then at annual intervals thereafter.

a. Quarterly periodic reports must be submitted within 30 days of the close of the quarter.

b. Annual periodic reports must be submitted within 60 days of the anniversary date of approval.

2. Determine if the periodic reports include the elements identified in 21 CFR 314.80(c)(2)(ii) and 600.80(c)(2)(ii), including a history of actions taken, such as labeling changes or studies initiated, since the last report because of adverse drug experiences.

3. ICSRs submitted to FDA as part of a quarterly or annual Periodic Report may be submitted electronically in XML format through the Electronic Submissions Gateway (ESG), or on paper to the Central Document Room. Firms may not attach ICSRs in PDF-format to annual or quarterly Periodic Reports. During inspection, document the method used by the firm to submit ICSRs to the Agency with quarterly or annual Periodic Reports. If the firm has questions about electronic or paper submission of Periodic Reports to the Agency, refer the firm to the FDA FAERS website for instructions:

4. There are two exceptions to Periodic Reporting requirements:

   a. Periodic Reports are not required for OTC drugs marketed without an approval.

   b. Periodic Reports are not required for prescription drugs marketed without an approval under 21 CFR 310.305.

5. If the firm has a waiver permitting the submission of a "Periodic Safety Update Report" (PSUR) *in lieu* of the standard Periodic Report, determine if the PSUR has been submitted according to the established schedule. Determine if the PSUR contains the elements identified in The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Topic E2C (R1) "Periodic Safety Update Reports for Marketed Drugs"[4] (see PART VI, SECTION A, "REFERENCES" for FDA Guidance for industry on E2C (R1) reporting).

Q. NDA AND ANDA ANNUAL REPORTS

Determine if the firm is submitting Annual Reports for each of its products with an approved NDA or ANDA as required by 21 CFR 314.81(b)(2).

Verify all sections are included and the Annual Reports are being submitted in a timely

[4] Note: In December 2010, the ICH Steering Committee approved the development of a new ICH E2C (R2) Guideline to replace the current E2C (R1) "Periodic Safety Update Reports for Marketed Drugs". The new ICH E2C (R2) document was not finalized as of the date of this CPGM.

manner. Firms are required to submit Annual Reports to FDA within 60 days of the anniversary date of approval of the application. In some cases, the Agency may require the firm to submit these reports at different times.

R. PADE REPORTING REQUIREMENTS FOR OTC MONOGRAPH DRUGS

Determine if the firm has non-application, nonprescription drugs, also known as OTC Monograph drugs. If so, determine if the firm is complying with the Nonprescription Drug Consumer Protection Act (Section 760 of the FD&C Act). Requirements of the Nonprescription Drug Consumer Protection Act (Section 760 of the FD&C Act) include:

1. All serious events must be reported to FDA, not just serious and unexpected events.

2. All reports must be expedited. ICSRs for serious, domestic adverse events for OTC monograph products must be submitted to the Agency within fifteen business days.

3. OTC drugs marketed in the United States without an approved application have no requirement to submit foreign adverse experience reports to the Agency.

4. Reports must be accompanied by a copy of the label on or within the retail package.

5. The Nonprescription Drug Consumer Protection Act (Section 760 of the FD&C Act) does not specifically require firms to have adequate written procedures covering PADE reporting for OTC monograph products. In the absence of such written procedures, determine how the firm assures that complete, accurate, and timely PADE reports are submitted to FDA.

6. Periodic Reports are not required for OTC drugs marketed without an approval.

7. The Nonprescription Drug Consumer Protection Act (Section 760 of the FD&C Act) does *not* apply to OTC drugs marketed *with* an approved application. OTC Drugs marketed with an approved application must comply with the reporting requirements in 21 CFR 314.80.

   To aid industry compliance with the Dietary Supplement and Nonprescription Drug Consumer Protection Act, FDA has published a guidance document entitled "Guidance for Industry - Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application."

S. ELECTRONIC SUBMISSIONS

Determine if the firm is voluntarily participating with FDA's program to provide postmarketing regulatory submissions in electronic format. Reports submitted electronically are subject to the same reporting deadlines as paper reports, as well as the 21 CFR Part 11

standards that apply to the electronic system managing the data. Contact the AERS Electronic Submission Coordinator at the following telephone number or e-mail address to discuss issues related to electronic submission of adverse event data.

Phone: (301) 918-9580
Fax: (301) 918-3134
E-mail: AERSESUB@CDER.FDA.GOV

T. PART 11 COMPLIANCE

All electronic technology systems for collection, processing, evaluation, review, management, or submission of adverse event data should comply with federal standards for data management under 21 CFR Part 11. These requirements address electronic records, open and closed systems, digital signatures, electronic records, electronic signatures, and other controls.

U. PADE COLLECTION & REPORTING BY NON-APPLICANTS

Ask the firm if it out-sources any portion of its PADE reporting process to a contractor or affiliate. If any part of the firm's adverse event reporting process is not being performed directly by the firm, proceed as follows:

1. Collect the name, address, and telephone number of any contractors or affiliates involved in PADE reporting activities with the firm. Identify all domestic and international locations where PADE reports are processed for submission to FDA on behalf of the firm. Obtain the name of a responsible person at the contractor's location.

2. Obtain and review a copy of the written agreement between the firm and its contractor for adverse event processing. If the firm is reluctant to provide you with a copy of the contract, tell the firm that they may redact any financial information in the contract. During PADE inspections, the Agency is interested in scope of work only.

3. Read the contract and determine the scope of work and responsibilities of each party. Determine what PADE reporting activities are being performed at each location. Specify the products for which each location processes PADEs.

4. Determine the party responsible for maintaining the drug safety database. Determine the physical address where the drug safety database is located.

5. For non-applicant manufactures, packers or distributors whose name appears on the label, verify that all serious PADE reports are submitted to the applicant within five calendar days. Non-applicant manufacturers, packers or distributors who do not submit serious and unexpected PADEs to the applicant within five calendar days, are required to submit them to the Agency within fifteen (15) calendar days.

V. FDA-483, INSPECTIONAL OBSERVATIONS

1. Observed deviations from regulations should be documented on Form FDA 483, Inspectional Observations, using TURBO EIR. TURBO EIR citations may be found under CFR 314.80, 314.98, 310.305, and Section 760.

2. Questions about the firm's labeling, medical evaluations of PADE reports, or adherence to FDA guidance documents can be discussed with the firm and included in the EIR, but not cited on the Form FDA 483. If the Investigator questions whether an observation should be a discussion item with the firm's management, or a deviation documented in the FDA Form 483, contact the PVC Team.

W. ESTABLISHMENT INSPECTION REPORT (EIR)

The Investigator should refer to the Investigations Operations Manual (IOM), subchapters 5.5.7 "ADVERSE EVENT REPORTING/ Risk Evaluation and Mitigation Strategies (REMS)" and subchapter 5.10 "REPORTING" for guidance on reporting of inspectional findings.

1. The PADE EIR does not require full and detailed narratives for every subsection under 5.10 of the IOM. For example, sections on Interstate Commerce, Manufacturing Codes, and Recall Procedures are not applicable in a PADE EIR.

2. Information contained in the EIR may be used to support a regulatory or administrative action. The EIR and exhibits must clearly document all findings that could significantly impact the decision-making process and include sufficient information to support the recommended classification. For those EIRs that will be used to support a recommendation for regulatory action, the report must include the following information for each drug product implicated in the recommended action:

   a. The drug product's brand or generic name and its NDA or ANDA number.

   b. The NDA of ANDA approval date.

   c. Labeling (including package inserts) in use at the time of the report for the drug product covered during the inspection.

   d. The date used by the firm as the basis for determining reporting cycles under the periodic reporting requirements, if other than the NDA or ANDA approval date, and a copy of the FDA approval of this alternate date.

   e. The conditions and effective date(s) of any waivers granted to the firm by FDA.

   f. The time periods during which the PADE reports covered by the inspection were received by the firm, and the dates the firm submitted the reports to the agency.

3. The endorsement to the EIR should provide a summary of the major deficiencies noted during the inspection, whether corrective actions that were promised or implemented by the firm, and the district's classification of the inspection.

X. SAMPLE COLLECTION

Sample collections are not planned under this program.

Y. POST-INSPECTION COMMUNICATIONS

1. The District should submit in CMS, if applicable, or forward by email to the PVC Team, any post-inspection communications with the firm concerning corrective actions.

2. If post-inspection meetings with the firm are planned, request notifying the PVC Team at least two weeks in advance of the meeting at CDER-OSI-ADE@FDA.HHS.GOV.

3. For foreign inspections, Investigators should instruct the firm to submit any written response to the inspection directly to CDER's Office of Compliance, Pharmacovigilance Team, and copy the Investigator.

PART IV - ANALYTICAL

No analytical activities are planned under this program.

PART V – REGULATORY AND ADMINISTRATIVE STRATEGIES

Inspectional findings documenting that a domestic or foreign firm's PADE reporting is not in a state of control may be used as evidence for taking appropriate advisory, administrative, and/or judicial actions. Regulatory action recommendations and supporting documents (such as the draft Warning Letter, EIR, and exhibits to the EIR) should be forwarded electronically by the recommending district, via CMS, to the PVC Team in CDER Office of Compliance, Office of Scientific Investigations (OSI). The recommending district will be responsible for drafting, developing, and issuing all domestic Warning Letters. OSI will be responsible for the final classification of inspections, and authoring and issuing all foreign Warning Letters.

The District Office should consult with OC's PVC Team when a regulatory action recommendation is considered to allow for discussion of the recommendation and resolution of any early concerns or questions relating to the case. Once the recommendation is received by OSI, the responsible CSO will review the recommendation packet and discuss any significant concerns or revisions with the District Compliance Officer. After OC clearance, OSI will forward the regulatory action recommendation to the Office of Chief Counsel for its review and approval, if applicable. The final approved version of the document will be returned to the district for signature by the District Director and issuance to the firm.

A. WARNING LETTERS

The issuance of a Warning Letter (WL) may be warranted when the inspection uncovers significant objectionable conditions, such as those listed below (others may apply), which impact the ability of FDA safety reviewers to properly evaluate the safety of marketed drugs. The observations listed below do not necessarily warrant the issuance of a WL to a firm. All WL recommendations will be evaluated on a case-by-case basis by the PVC Team and OSI management.

1. Failure to develop written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences;

2. Failure to submit PADE reports for serious and unexpected adverse drug experience events;

3. Failure to submit periodic reports or NDA annual reports for drugs with approved applications;

4. Submission of incomplete and/or inaccurate periodic reports or NDA annual reports;

5. Reporting serious, unlabeled events associated with the use of approved drug products as part of a periodic report instead of under separate cover as 15-day alert reports;

6. Failure to submit 15-day initial and follow-up reports on time;

7. Failure to submit 15-day reports derived from a post-marketing study where there is a reasonable possibility that the drug caused the adverse drug experience;

8. Submission of inaccurate and/or incomplete 15-day alert reports and follow-up reports;

9. Failure to conduct prompt and adequate follow-up investigations into adverse drug experiences that are the subject of post-marketing 15-day alert reports; and

10. Failure to maintain complaint records for marketed drugs and failure to maintain PADE records.

B. UNTITLED LETTERS

An Untitled Letter (UL) may be warranted when the deficiencies found at the firm are severe enough to justify a formal letter to the firm, but do not meet the threshold of regulatory significance for a Warning Letter. Factors that influence whether or not a WL or UL are issued include the nature and extent of the violations (e.g., repeated or deliberate), the compliance history of the inspected firm, and the corrective actions implemented by the firm. For all WLs and ULs, the Districts are to follow the guidance and procedures relating to the preparation and issuance of advisory actions that are set forth in the Regulatory Procedures Manual (RPM 4-2-1).

C. RESPONSES & CORRECTIVE ACTIONS

Warning letter responses, corrective action plans, and the implementation of these corrections should be reviewed and monitored by the District Office. If the response or corrective actions are inadequate, or if no response is received, then the District Office should begin follow-up action as necessary to achieve correction. If the response appears adequate, then the District Office will verify that commitments have been fulfilled and that correction has been achieved, and will notify other appropriate agency units. If necessary to ensure that corrections have been implemented, follow-up inspections should be conducted promptly after the agreed-upon date of completion of the promised corrections. The District Office is encouraged to notify the PVC Team at least 2 weeks prior to issuing a follow-up assignment in FACTS under PAC 53001B to receive additional information. The District Office should notify the PVC Team at CDER-OSI-ADE@FDA.HHS.GOV.

If incomplete corrections were made by the firm following a WL or UL, and the existing violations do not warrant enforcement action, Districts should consider holding a regulatory meeting with the firm.

D. ENFORCEMENT ACTIONS

The following enforcement actions may be considered if incomplete corrections were made by the firm following a WL or UL, and if the existing violations meet the level of

significance described below.

1. Injunction: Injunction should be considered when follow-up inspection(s) show that the firm has a continuing pattern of significant and substantial deviations despite previous attempts by FDA to obtain compliance.

2. Seizure: Seizure for failure to comply with postmarketing adverse drug experience reporting regulations would only be possible if the approval of the application for the product has first been withdrawn [Food, Drug, and Cosmetic Act, Section 304(a)(1)]. Seizure would then be based on distribution of an unapproved drug product.

3. Prosecution: Evidence that a firm is submitting false information, not submitting required reports for serious PADEs, or withholding important information, the submission of which may have resulted in the Agency requiring labeling changes or withdrawing an application, should be assessed against the Agency's Application Integrity Policy. Evidence of this activity may warrant referral to the Office of Criminal Investigations (OCI) for consideration of prosecution.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. REFERENCES

1. FDA Laws, Regulations, and Directives

   a. Federal Food, Drug, and Cosmetic Act
   http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/default.htm – Sections 301(e), 302, 303, 304(a)(1), 505(e), 505(k), 756, and 760.

   NOTE: Section 760, added by the Dietary Supplement and Nonprescription Drug Consumer Protection Act, Dec 2006
   http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148035.htm.

   b. 21 CFR http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm Sections 211.198, 310.305, 314.80,314.81, 314.98, 314.540, and 600.80

   c. Final Rule & Correction: "Expedited Safety Reporting Requirements for Human Drug and Biological Products" (62 FR 52237, October 7, 1997 & 63 FR 14611, March 26, 1998) https://www.federalregister.gov/articles/1997/10/07/97-26255/expedited-safety-reporting-requirements-for-human-drug-and-biological-products and https://www.federalregister.gov/articles/1998/03/26/98-7833/expedited-safety-reporting-requirements-for-human-drug-and-biological-products-correction.

   d. Final Rule: "Postmarketing Expedited Adverse Experience Reporting for Human Drugs and Licensed Biological Products: Increased Frequency Reports" (62FR 34166 June 25, 1997) http://www.federalregister.gov/articles/1997/06/25/97-16684/postmarketing-expedited-adverse-experience-reporting-for-human-drug-and-licensed-biological-products.

   e. Regulatory Procedures Manual, Chapters 4, 5, 6, and 10. (Note: FDA Staff should use intranet "RPM Master List" on FDA intranet)
   http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm.

   f. Investigations Operations Manual, Subchapters 5.2, 5.5, 8.2, and 8.4
   http://www.fda.gov/ICECI/Inspections/IOM/default.htm.

2. FDA & ICH Guidances

   a. FDA Guidance for Industry: Guideline for Postmarketing Reporting of Adverse Drug Experiences, March 1992
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM299138.pdf.

   b. FDA Guidance for Industry: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report,

August 1997
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071981.pdf.

c. FDA Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, March 2001
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080538.pdf.

d. FDA Guidance for Industry: Labeling of Nonprescription Human Drug Products Marketed without an Approved Application as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act: Questions and Answers, September 2009
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM180790.pdf.

e. FDA Guidance for Industry: Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed without an Approved Application, July 2009 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm171672.pdf.

f. ICH Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A Guideline), March 1995
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129518.pdf.

g. ICH Tripartite Guideline: Topic E 2 C (R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (Step 5), June 1997
http://www.emea.europa.eu/pdfs/human/ich/028895en.pdf.

h. FDA Guidance for Industry: ICH E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, November, 1996
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073102.pdf

i. FDA Guidance for Industry: E2B(M) Data Elements for Transmission Of Individual Case Safety Reports (ICH Revision 2), March 2005
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129434.pdf.

3. Websites and Databases

a. FDA Training & Continuing Education website "Field Investigators: Adverse Drug Effects (ADE) Detectives (2000)" (Video contains relevant information for ADE inspections) http://www.fda.gov/Training/ForHealthProfessionals/ucm091001.htm.

b. FDA Adverse Event Reporting System website "FDA Adverse Event Reporting System (FAERS) (formerly AERS)" http://www.fda.gov/cder/aers/default.htm.

c. FDA MedWatch website "MedWatch: The FDA Safety Information and Adverse Event Reporting Program" http://www.fda.gov/medwatch/index.htm.

d. FDA Inspections, Compliance, Enforcement, and Criminal Investigations website "Application Integrity Policy"
http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm.

e. FDA Drug Database "Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations" http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

f. FDA Drug Database "National Drug Code Directory"
http://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm

g. FDA Drug Database: "Drugs@FDA"
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

h. FDA Database: "Postmarketing Requirements and Commitments"
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

i. Partnership for Prescription Assistance.
http://www.pparx.org/en/prescription_assistance_programs/list_of_participating_programs.

B. ATTACHMENTS

Attachment A: Sample MEDWATCH form, FDA Form 3500A; see
http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf

Attachment B: Sample Council for International Organizations of Medical Sciences, Suspect Adverse Reaction Report Form (CIOMS Form I); see http://www.cioms.ch/index.php/cioms-form-i.

C. CONTACTS

See FACTS Assignment for specific points of contact.

1. CDER Office of Compliance, Office of Scientific Investigations,

   a. PVC Team Program Contacts are:

▪ Kevin Prohaska, Director	(301) 796-3707	Kevin.Prohaska@fda.hhs.gov
▪ Tamika White, (Acting) Branch Chief	(301) 796-3224	Tamika.white@fda.hhs.gov
▪ LaKisha Williams, Team Leader	(301) 796-5258	LaKisha.Williams@fda.hhs.gov
▪ Marcia Gelber, CSO	(301) 796-3889	Marcia.Gelber@fda.hhs.gov
▪ Yusuf Henriques, CSO	(301) 796-5492	Yusuf.Henriques@fda.hhs.gov
▪ Maureen Melvin, CSO	(301) 796-5366	Maureen.Melvin@fda.hhs.gov
▪ Donna Stewart, Program Spec.	(301) 796-3219	Donna.Stewart@fda.hhs.gov

b. PVC Team e-Mail Account: CDER-OSI-ADE@FDA.HHS.GOV

c. Mailing address for PVC Team:

Pharmacovigilance Compliance Team (PVC)
Division of Safety Compliance, Office of Scientific Investigations
Office of Compliance, CDER
Food and Drug Administration
10903 New Hampshire Ave.
WO 51, Room 4248
Silver Spring, Maryland 20933-0002

Fax (301) 847-8748

d. A complete organizational chart for the CDER Office of Compliance, Office of Scientific Investigations is available on the FDA intranet at CDER > OFFICE OF COMPLIANCE > OFFICE OF SCIENTIFIC INVESTIGATIONS | "ORGANIZATIONAL CHART."

2. Office of Regulatory Affairs (ORA) Contacts

OMPTO / Division of Medical Products and Tobacco Program Operations

- James Dunnie, Drug Program Expert 301-796-5438
- Ann Marie Montemurro, Director 301-796-5521

PART VII - CENTER RESPONSIBILITIES

A. For all inspections

The Office of Compliance, OSI PVC Team will:

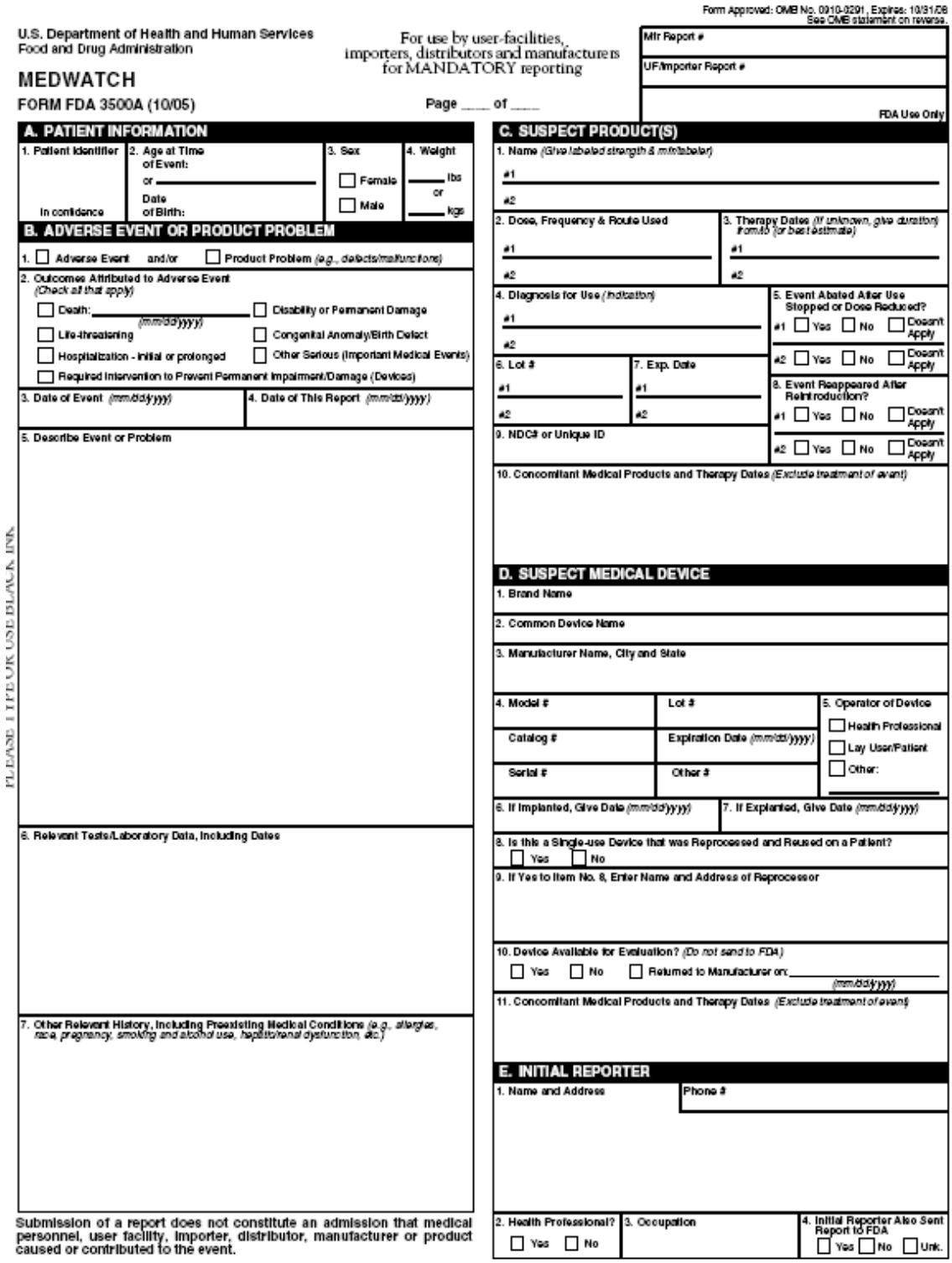
1. Assess compliance issues related to possible deviations and violations of PADE requirements.
2. Identify, prepare, issue, and monitor all CDER-initiated inspectional assignments.
3. Communicate specific PADE reporting concerns, if any, to Investigators prior to inspection.
4. Serve as the POC for field inquiries on PADE assignments and compliance issues.
5. Provide guidance and support to the field during all phases of inspections, investigations, and regulatory actions.
6. Review and evaluate OAI establishment inspection reports and regulatory recommendations from District Offices.
7. Submit approved regulatory recommendations to the Office of Chief Counsel, if required.
8. Act as the liaison between ORA and OSE or OND for the review and evaluation of medical and epidemiological aspects of field inspectional findings.
9. Notify OSE and OND of any significant PADE reporting problems and/or violations.

B. For foreign inspections

The Office of Compliance, OSI PVC Team will

- review the firm response, if any,
- determine adequacy of the response, and
- issue Warning Letters or Untitled Letters, as appropriate.

See http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf



Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (10/05)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr Report #
UF/Importer Report #
FDA Use Only

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy)
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☐ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)
3. Date of Event (mm/dd/yyyy)
4. Date of This Report (mm/dd/yyyy)
5. Describe Event or Problem
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & manufacturer)
#1
#2
2. Dose, Frequency & Route Used
3. Therapy Dates (If unknown, give duration) From/To (or best estimate)
4. Diagnosis for Use (Indication)
5. Event Abated After Use Stopped or Dose Reduced? ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot #
7. Exp. Date
8. Event Reappeared After Reintroduction? ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# or Unique ID
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # | Lot # | Catalog # | Expiration Date (mm/dd/yyyy) | Serial # | Other #
5. Operator of Device ☐ Health Professional ☐ Lay User/Patient ☐ Other:
6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. INITIAL REPORTER

1. Name and Address
Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☐ Unk.

PLEASE TYPE OR USE BLACK INK

MEDWATCH

FORM FDA 3500A (10/05) *(continued)* Page ____ of ____

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. Check One ☐ User Facility ☐ Importer
2. UF/Importer Report Number
3. User Facility or Importer Name/Address
4. Contact Person
5. Phone Number
6. Date User Facility or Importer Became Aware of Event *(mm/dd/yyyy)*
7. Type of Report ☐ Initial ☐ Follow-up # ____
8. Date of This Report *(mm/dd/yyyy)*
9. Approximate Age of Device
10. Event Problem Codes *(Refer to coding manual)* Patient Code ___ - ___ - ___ Device Code ___ - ___ - ___
11. Report Sent to FDA? ☐ Yes ____ *(mm/dd/yyyy)* ☐ No
12. Location Where Event Occurred ☐ Hospital ☐ Home ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Outpatient Diagnostic Facility ☐ Ambulatory Surgical Facility ☐ Other: ____ *(Specify)*
13. Report Sent to Manufacturer? ☐ Yes ____ *(mm/dd/yyyy)* ☐ No
14. Manufacturer Name/Address

G. ALL MANUFACTURERS

1. Contact Office - Name/Address *(and Manufacturing Site for Devices)*
2. Phone Number
3. Report Source *(Check all that apply)* ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other: ____
4. Date Received by Manufacturer *(mm/dd/yyyy)*
5. (A)NDA # ____ IND # ____ STN # ____ PMA/510(k) # ____ Combination Product ☐ Yes Pre-1938 ☐ Yes OTC Product ☐ Yes
6. If IND, Give Protocol #
7. Type of Report *(Check all that apply)* ☐ 5-day ☐ 30-day ☐ 7-day ☐ Periodic ☐ 10-day ☐ Initial ☐ 15-day ☐ Follow-up # ____
8. Adverse Event Term(s)
9. Manufacturer Report Number

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Other: ____
2. If Follow-up, What Type? ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. Device Evaluated by Manufacturer? ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code: ____
4. Device Manufacture Date *(mm/yyyy)*
5. Labeled for Single Use? ☐ Yes ☐ No
6. Evaluation Codes *(Refer to coding manual)* Method ___ - ___ - ___ - ___ Results ___ - ___ - ___ - ___ Conclusions ___ - ___ - ___ - ___
7. If Remedial Action Initiated, Check Type ☐ Recall ☐ Repair ☐ Replace ☐ Relabeling ☐ Notification ☐ Inspection ☐ Patient Monitoring ☐ Modification/Adjustment ☐ Other: ____
8. Usage of Device ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. If action reported to FDA under 21 USC 360(i), list correction/removal reporting number:
10. ☐ Additional Manufacturer Narrative and / or 11. ☐ Corrected Data

The public reporting burden for this collection of information has been estimated to average 66 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration - MedWatch
10903 New Hampshire Avenue
Building 22, Mail Stop 4447
Silver Spring, MD 20993-0002

Please DO NOT RETURN this form to this address.

OMB Statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

See http://www.cioms.ch/index.php/cioms-form-i.

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	